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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/630,333	07/31/2000	Anand C. Burman	U 012799-1	5586

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 05/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/630,333	BURMAN ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 21-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-12 and 21-30* is/are allowed.

6)☒ Claim(s) *13 and 31-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1-13 and 21-40 are pending.

Applicants' amendment filed February 24, 2004 is acknowledged. Applicants' response has been fully considered. Claims 10-13 have been amended, and claims 14 and 41-50 have been cancelled. Therefore, claims 1-13 and 21-40 are examined.

Objection Withdrawn

2. The previous objection of claims 12 and 13 is withdrawn in view of applicants' amendment the claim in the amendment filed February 24, 2004.

Rejection Withdrawn

Claim Rejections-Obviousness Type Double Patenting

3. The previous rejection of claims 1, 12, 13, 31 and 41 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 5, 6, 8, 11-14, 17, 18, 20, 22-24, 63, 64, 67, 68, 70, 72-74, 327 and 328 of copending application No. 09/896,903, is withdrawn in view of the terminal disclaimer filed, and applicants' response at page 7 in the amendment filed February 24, 2004.

Claim Rejections - 35 USC § 112

4. The previous rejection of claims 14 and 41-50, under 35 U.S.C.112, first paragraph, is withdrawn in view of applicant's cancellation of the claim in the amendment filed February 24, 2004.

5. The previous rejection of claims 10, 11, 14 and 41-50, under 35 U.S.C.112, second paragraph, is withdrawn in view of applicants' amendment to the claim, applicant's cancellation of the claim, and applicants' response at page 7 in the amendment filed February 24, 2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 13 and 31-40 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating various human cancer cell lines *in vitro* by administering a peptide of formula, X-D-Phe-Gln-R1-R2-Val-R3-His-R4-NH_2 or of SEQ ID NO:3-11 or 12, does not reasonably provide enablement a method for treating various cancers of colon, lung, prostate, stomach, laryngeal, oral, breast, duodenum, ovarian, pancreatic, leukemia or glioblastoma in mammals by administering a peptide of formula, X-D-Phe-Gln-R1-R2-Val-R3-His-R4-NH_2 or of SEQ ID NO:3-11 or 12. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 13 and 31-40 encompass a method for treating various cancers of colon, lung, prostate, stomach, laryngeal, oral, breast, duodenum, ovarian, pancreatic, leukemia or glioblastoma in mammals by administering a peptide of formula, X-D-Phe-Gln-R1-R2-Val-R3-His-R4-NH_2 or of SEQ ID NO:3-11 or 12. The specification, however, only discloses cursory conclusions (page 4, lines 6-9; page 8, lines 1-5) without data supporting the findings, which state that the present invention describes the preparation of peptide analogs of bombesin/gastrin

releasing peptide (GRP) using constrained amino acids, and the use of the peptide in cancer therapy. There are no indicia that the present application enables the full scope in view of a method treating various cancers using the peptide analogs of bombesin/GRP as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the presence or absence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding the treating conditions for treatment of various cancers in mammals and the effects of the peptide analogs of bombesin/GRP for in vivo treatment, which are not adequately described or demonstrated in the specification.

(2). The presence or absence of working examples:

The specification demonstrates the treatment of various human cancer cell lines with the peptide of formula, X-D-Phe-Gln-R1-R2-Val-R3-His-R4-NH_2 in vitro (Examples 12-14). However, there are no working examples indicating the in vivo treatment of various cancers in mammals using the claimed peptide, nor demonstrating the effect of the claimed peptide.

(3). The state of the prior art and relative skill of those in the art:

The related art (references shown at pages 1-4 of the specification) indicates analogs of bombesin/GRP have anti-tumor activity in vitro or in vivo, however, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the treating conditions such as the dose and the effect for the treatment of various cancers in vivo using the claimed peptide to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims are directed to a method for treating various cancers in mammals using the claimed peptide. The specification indicates the claimed peptide shows cytotoxicity in the treatment of various human cell lines (Experiments 12-14), however, the percentage of cytotoxicity for various peptides appears not concentration dependent, e.g., SEQ ID NO:11 has 24.2% cytotoxicity at 1 μM, 31.9% cytotoxicity at 10 nM, and 21.6% cytotoxicity at 10 pM against KB cell; and 18.6% cytotoxicity at 1 μM, 25.7% cytotoxicity at 10 nM, and 19.7% cytotoxicity at 10 pM against PTC cells (see the table at page 21). Since the cytotoxicities of peptides against various cancer cells are not concentration dependent, it is not clear how to extrapolate the in vitro data to in vivo effect. Furthermore, the specification does not provide teachings for in vivo treatment of various cancers, thus, the effect of the peptide in the claimed method is highly unpredictable.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method for treating various cancers in mammals using the claimed peptide. The specification indicates the cytotoxicity of the peptide for in vitro treatment

(see Examples 12-14), it does not indicate the in vivo treating conditions such as the amount of the peptide administered and the time required for the treatment, nor demonstrates the in vivo effects of the peptide. Moreover, the in vitro data indicates the cytotoxicity of the peptide is not concnetration dependent (see the section of unpredictability), there are no teachings on how to extrapolate the in vitro data to in vivo treatment, and no working examples are provided for in vivo treatment. Since the specification does not provide sufficient teachings on the in vivo treatment, and how to extrapolate the in vitro data to in vivo effect, thus, it is necessary to carry out further experimentation to assess the effect of the peptide for in vivo treatment.

(6). Nature of the Invention

The scope of the claim includes a method for treating various cancers in mammals using the claimed peptide, however the specification has not provided sufficient teachings in the treatment, nor has demonstrated the effect of the claimed peptide for in vivo treatment. Thus, the disclosure is not enabling for reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed methods, and the teaching in the specification is limited, the effect of the claimed peptide is unpredictable, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effects of the claimed peptide in treating various cancers in mammals.

In response, applicants indicate the specification discloses the peptides of SEQ ID NOs: 3-12 are cytotoxic to one or more cancer cell lines: colon, lung, prostate, stomach, laryngeal, oral, breast, duodenum, ovarian, pancreatic, leukemia or glioblastoma, which are the types of cancer in claims 13 and 31-40; the Declaration of Dr. Rama Musherjee provides a peptide of this

invention treats cancer in vivo, and applicants have filed references which establish the correlation between in vitro and in vivo activity; and MPEP 2164.02 states that only an enabling disclosure is required and applicants need not describe all actual embodiments, and based on the relevvant evidence as a whole, there is reasonable correlation between the disclosed in vitro utility and in vivo activity, conseidering it is well known to use the in vitro models to test compounds for anticancer activity and that one skilled in the art knows how to use these test results for in vivo treatment, thus applicants conclude claims 13 and 31-40 are enabled (pages 7-8 of the response). The response and the declaration have been fully considered, however, the argument is not found persuasive because the in vivo data shown in the declaration only indicates a specific peptide, SEQ ID NO:11 out of 60+ peptides has some anti-tumor activity toward an animal model having colon adenocarcinoma xenografts, there are no data indicating the in vivo treatment of various cancers using different peptides, which are encompassed by the claims, and the specification does not provide any teachings how the in vivo effect can be predicted from the in vitro data. Although applicants indicate how the in vivo dose used for SEQ ID NO:11 are correlated to the in vitro dose in the xenograft model, it appears the in vivo effect cannot be predicted from the in vitro data considering the the cytotoxicity of the peptide is not concnetration dependent (see the section of unpredicatablility). Regarding the determination of a starting dose in humans from animal data, the references do provide allometric conversions of animal to humans. Since the specification and the declaration have not provided sufficient teachings for in vivo treatment of various cancers using the claimed peptides, and the correlation of the in vitro and in vivo activity, it is necessary to have further experimentation to assess the effects of various peptides in the treatment of various cancers in mammals.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 13 and 31-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 13 and 31-40 are indefinite because the claim lacks an essential step in the method of treating cancer in mammals. The omitted step is the outcome of the treatment.

In response, applicant has amended claim 13 citing "effective to treat the cancer". The response has been fully considered, however, the term "effective to treat the cancer" does not reflect the endpoint of the treatment.

Conclusions

8. Claims 13 and 31-40 are rejected. It appears claims 1-12 and 21-30 are free of prior art and allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

CHRISTOPHER S. F. LOW
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May 7, 2004